Remarks

Introduction

Receipt is acknowledged of the Office Action dated June 4, 2002 (Paper No. 16). Claims 1-19 and 46-48 are pending and active in this case.

Election/Restriction

In the Office Action mailed 12/18/2001, the Examiner asserted that the instant invention lacks Unity of Invention because Claim 1 allegedly "does not provide a technical feature that is distinguished over the prior art, as evidenced by an NCBI blast search which shows the 1988 submission of a CEA precursor protein which comprises the sequence YRSGENLNL at positions 249-257." The Examiner pointed out that "YRSGENLNL has at least one amino acid substitution at a non MHC anchor position and absent evidence to the contrary acts as an agonist." Applicants traversed the restriction requirement that the Examiner required in that office action, arguing that the invention does, in fact, have Unity of Invention, providing a thorough analysis of the issue, complete with relevant citations to the MPEP. In the Office Action mailed 6/4/2002, the Examiner found Applicant's traversal unpersuasive, and made the restriction final, on the basis that "unity of invention is broken upon the citation of prior art." As this statement was not further explained and Applicant can find no suggestion in either the MPEP or 37 CFR to suggest that the citation of prior art breaks the Unity of Invention, Applicants assume that the Examiner is reiterating the argument that the invention does not provide a technical feature that is distinguished over the prior art, as evidenced by the above-mentioned NCBI blast search. As discussed below, however, this sequence does not anticipate claim 1 and the instant invention does, therefore, distinguish over the prior art. Accordingly, Applicants respectfully request reconsideration of the restriction requirement and rejoinder of claims 20-45 and 49-50 as there is Unity of Invention in this case.

Priority Claim

Applicants thank Examiner for pointing out that claim to priority was not explicit in the specification. The amendment to the specification makes such claim and adds no new matter.

Drawings

The Examiner has required submission of new formal drawings in accordance with the draftsman review Form PTO 892. Those drawings are submitted concurrently with this reply. The new drawings add no new matter to the application.

Abstract

An abstract of the disclosure is attached hereto, on a separate sheet, as required by the examiner.

Claim Rejections Under 35 U.S.C. § 112

On pages 4-5 of the Action, Examiner rejects claims 1-5, 7-19 and 46-48 as allegedly not enabled for a "peptide agonist comprising any amino acid substitution of any anchor position(s) of SEQ ID NO:1 with increased immunogenicity." Applicant's presume that Examiner intended to recite "non-anchor" rather than "anchor" position(s), according to the claims. Specifically, the Examiner objects to the "comprising" language of the claim and suggests that the claims are only enabled if written as "consisting." The Examiner cites Janeway et al (Immunobiology 4th Edition (1999) page 121) for the proposition that CTLs recognize MHC class I peptides wherein said peptides are between 8 and 10 amino acids long. The Examiner concludes from this reference that "one of skill would not be able to predict which amino acids could be added to the nonamers with the amino acid sequence of SEQ ID NO:2, 3, 4, or 5, such that said peptides retained their agonistic activity without additional guidance from the specification."

This reference, however, also specifically recognizes that peptides of greater length than 8-10 amino acids may bind within the groove of MHC class I molecules. The reference provides two mechanisms by which the longer peptide may bind. They may be accommodated by a "kinking" in the peptide backbone, or the peptide may extend out of the groove at the carboxy terminus. Further, the reference indicates that most peptides of suitable length will properly bind

to the MHC class I molecules so long as the anchor residues are in their proper places. Therefore, there is no need to limit the scope of the claims to sequences consisting of SEQ ID NO: 2, 3, 4 and 5.

The Examiner asserts that because Applicants screened 80 peptides for agonistic activity and only 5 were found to have such activity, one of skill in the art would not be able to predict which peptides comprising a peptide with one or more substitutions in non anchor positions of SEQ ID NO: 1 would be agonists. The Examiner further asserts that it would require undue experimentation for one of skill to predict which non MHC anchor positions of SEQ ID NO:1 could be substituted because the non-anchor positions of peptides that bind different class I molecules can vary.

In determining the propriety of a rejection based upon the scope of the claim relative to the scope of enablement, one must consider whether one of skill in the art could make and use the entire scope of the claimed invention without undue experimentation. MPEP §2164.08 (August 2001). However, "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction which the experimentation should proceed." MPEP §2164.06 (August 2001) citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.. 1988) (emphasis added). The experimentation needed to determine whether a given substitution would affect the agonistic activity of a peptide in this case is minimal, and well within the skill of an artisan. Male *et al* (Advanced Immunology 2nd Edition (1991) page 5.11) teach that "[t]he effects of amino-acid substitutions at each position of an immunogenic peptide on MHC antigen binding or on stimulation of functional T cells can be determined in order to classify an amino acid as making contacts with predominantly MHC antigen, TCR, both or neither. Armed with this information peptides have been docked into the MHC antigens groove in α-helical or extended conformations."

The decision in Ex parte Mark, 12 USPQ2d 1904 (Bd. Pat. App. Int. 1989) is particularly instructive here. The Mark appellants presented claims to a mutein of a "biologically active protein" where at least one cysteine residue that was "non-essential to said biological activity"

was "substituted by another amino acid." In reversing the examiner on enablement grounds, the Board reasoned that:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [the] declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the invention for a given protein. The fact that a given protein might not be amenable for use in the present invention in that the cysteine residues are needed for biological activity does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907.

The claims in Mark were quite broad because they pertained to **any** protein with **any** type of biological activity, whereas applicants' claims are directed to agonists of a stated sequence having recited properties. Moreover, appellant Mark's claims required a change in cysteine residues, which can drastic consequences on a protein due to the unique properties of cysteine in its function of forming disulfide bonds. If a cysteine residue in a given protein is involved in the formation of disulfide bonds, removing that cysteine residue would change the three-dimensional structure of the protein. The claims in Mark, which were considered enabled by the Board, required the skilled artisan to determine which cysteine residues could be removed ***in any given*** protein without adversely impacting the three-dimensional structure of the protein.

Applicants submit here that the Board applying the logic of Mark would consider the claims enabled, particularly in view of the fact that Applicants screened 80 peptides for their effect on agonistic activity, replacing each of positions 5-8 with all 20 natural amino acids. In view of Applicants' teaching, it is clear that such efforts are routine within the art.

The Examiner also has rejected claims 1-5, 7-19 and 46-48 under 35 USC §112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that

only a partial structure of the agonist is recited "since the anchor positions can be any amino acid, including naturally occurring amino acids, and also non naturally occurring amino acids." However, this is factually inaccurate. The specification at both page 5 and pages 33-34 indicate that positions 2 and 9 are the primary anchor sites and position 1 is a secondary anchor site. The residues for those sites are Leucine, Leucine, and Tyrosine respectively. The limitations of the claims do not allow for substitution of these positions. The Examiner further asserts that because the transitional term "comprising" is used in the claims, an indeterminate number and type of additional amino acids are encompassed within the claims, and therefore the claim is not adequately described. The term comprising is a term of art that leaves "the claim open for the inclusion of unspecified ingredients even in major amounts." MPEP §2111.03 citing Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948). This is a well recognized convention and in no way renders the claim inadequately described. The Examiner has not met the burden of showing why a person skilled in the art would not recognize in Applicants' disclosure a description of the invention defined by the claims, as required by MPEP §2163.04. Having not met that burden, the description as filed is presumed to be adequate. Id.

The Examiner also asserts that there is no description of the required structural and specific agonistic functional features of the recited agonist, nor does the prior art disclose compensatory teachings to enable one of skill to identify the peptides encompassed , with the exception of SEQ ID NO: 2, 3, 4 and 5. However, according to the claims, the anchor positions are to remain unsubstituted and the modified agonist is to have "enhanced immunogenicity." Further, the specification discloses the method that Applicants used to screen 80 peptides for agonistic properties. Thus, the structural elements, the functional features, and the teaching to enable one of skill to identify peptides encompassed by the claims are all disclosed in the application.

The Examiner also rejects claims 1-5, 7-19 and 46-48 as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (applicants note here that paragraphs 11 and 12 of the office action appear to be identical and will thus not be addressed separately). The Examiner asserts that the claims recite

broadly "an agonist" and then recite "at least" which is a narrower statement of the range/limitation, thus rendering the claims indefinite.

Applicants respectfully point out that the proposition cited by the Examiner, as discussed in MPEP §2173.05(d) is inapplicable to the present claims. This rejection is appropriate in situations where the claim recites a broad range followed by "exemplary language" in the form of a narrower range or limitation. The examples cited by the MPEP, from the same cases cited by the Examiner, include "normal operating conditions such as while in the container of a proportioner." Id. citing Ex parte Steigerwald, 131 USPQ 74 (Bd. App. 1961). In such a case, it is unclear whether "while in the container of a proportioner" is merely exemplary of "normal operating conditions" or is a required limitation thereof. This concern does not apply to the instant claims. Claim 1 recites "[a] peptide comprising an agonist of a native sequence...wherein the agonist has at least one amino acid substitution at a non-MHC anchor position..." It is unambiguous from the plain language of the claim, that the phrase "at least one amino acid substitution..." is a required limitation of the claim and not merely exemplary language. This rejection is, therefore, inapplicable to the instant claims.

Rejections under 35 U.S.C. § 102

On page 10 of the Office Action, the Examiner rejects claims 1 and 2 under 35 U.S.C. 102(b) as allegedly anticipated by Barnett, T., Goebel, S.J., Nothdurft, M.A. and Elting, J.J. Genomics 3 (1), 59-66 (1988), according to an NCBI blast search (of record). The Examiner asserts that the reference teaches a CEA precursor protein which comprises the sequence YRSGENLNL at positions 249-257. The Examiner contends that YRSGENLNL has at least one amino acid substitution at a non MHC anchor position 5, and absent evidence to the contrary, the peptide acts as an agonist of SEQ ID NO:1.

Applicants note that while YRSGENLNL does, in fact, have a substitution at position 5, relative to SEQ ID NO:1, it also has a substitution at position 2, which is an anchor position. Because claims 1 and 2 do not allow for substitution of anchor positions, the cited sequence can not anticipate those claims.

Further, even if the cited sequence was not substituted at position 2, but had the native residue disclosed by SEQ ID NO:1, that sequence was found not to have agonistic effect. The Applicants screened 80 different peptides as disclosed in the specification. Among those 80, they substituted position 5 with all 20 natural amino acids, which would include the Glutamic acid disclosed in the cited sequence. At position 5, only Phenylalanine, Isoleucine, and Serine were found to provide stimulation, and all three were at reduced levels compared to SEQ ID NO:1 (see specification, page 35, lines 8-11).

Allowable subject matter

Applicants note with appreciation that the Examiner considers claim 6 allowable if rewritten to be independent and to include all of the limitations of the base claim and any intervening claims. Applicants assert that the rejections of all other claims have been overcome, and therefore allowance of all claims is earnestly solicited.

Conclusion

In view of the foregoing remarks, reconsideration of the application and allowance of all claims is respectfully requested. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the local exchange listed

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the first line of the specification on page 1 to read as follows:

This is a National Phase Application of PCT/US98/19794, filed 09/22/98, which claims the benefit of U.S. Provisional Application No. 60/061,589, filed 10/10/97.

ABSTRACT OF THE DISCLOSURE

The present invention relates to the preparation and use of peptides that act as agonists and antagonists of human carcinoembryonic antigen (CEA). Agonists of the CEA peptide, CAP1, are disclosed and their utility in enhancing immune responses against CEA demonstrated.